Alban Doran Esq.

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Jan. 16. /8

COLLOID DEGENERATION OF THE NON-CYSTIC OVARY, WITH ASSOCIATED VASCULAR CHANGES.[1]

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In a considerable number of ovaries, especially the ovaries of elderly women, the following appearances may be seen :—Thin sections examined with the naked eye by transmitted light reveal the presence of more or lest transparent spots of various shapes and sizes. Under the microscope these spots are found to be for the most part composed of a homogeneous material, semi-fluid or gelatinous: the smaller traversed in all directions by trabeculæ of the stroma, the larger clear in the centre, but showing stromal ingrowths at the circumference. The material contained in these spaces is unaffected by acetic acid; it is readily hardened by alcohol and other agents, which at the same time no further alter its appearance than by rendering it whitish and opaque when seen by reflected light, and by producing a certain amount of shrinking and cleavage. Thus satisfactory sections may be made from a hardened ovary and stained as desired. Hæmatoxylin gives good results: when a double staining is produced with hæmatoxylin and eosin, a very beautiful preparation may be obtained, the material of the softened patches being deeply coloured by the eosin, while the stroma and its prolongations take the logwood more especially. Carmine stains the new substance; picric acid does not affect it. Iodine produces no coloration.

Stained sections, mounted in glycerine, dammar, or Canada balsam, show that the very smallest patches, which are of microscopic dimensions, not exceeding the size of two or three undeveloped ovisacs, are usually irregularly oval, the long axis being determined by the general course of the tissue of the stroma. They are minutely subdivided by fine trabeculæ, which have all the appearance of being teased out, so to speak, by the accumulation of some substance within their meshes. These stromal trabeculæ consist of fibres and cells apparently quite unaltered, and in favourable specimens minute blood-vessels may be seen in them. The intruding material is structureless, resembling ground glass in appearance, and contains no trace of cells or nuclei. The spaces are bounded by the normal stroma, which shows no sign of condensation or any other change in their neighbourhood. There is no increased vascularity about the patches. The larger spaces can be shown in many cases to result from the fusion of several of the smaller: they are in all important respects identical with the latter; processes of fibro-cellular tissue run into them, accompanied by vessels, and the contained substance is microscopically similar. In some of the larger patches, however, the central parts show a new process of degeneration: instead of the cloudy material elsewhere observed, the centre is composed of coarsely granular *débris*, often associated with altered blood, the result of old extravasations. Moreover, the trabeculæ in these patches are commonly of considerable dimensions, but never completely traverse the spaces. It may be noticed here that in some of these larger degenerate structures, such as can be easily recognised with the naked eye, the boundary line of stroma may seem at first sight, when examined without the microscope, or with a very low magnifying power, to present a very distinct demarcation,—so distinct, in fact, as to resemble a cyst wall. Closer observation, however, will always show this appearance to be deceptive, and to be mainly produced by the shrinking of the new substance under the influence of the hardening agent. In the very largest patches, I have always found processes running inwards from the stroma, and the neighbouring tissue unaltered except by the existence of minute degenerate points such as those described above. There is never a trace of epithelial lining. In the more advanced stages, as in the earlier, there is an entire absence of increased vascularity; but there is a remarkable change in the blood-vessels, which will require a separate description. (In the figure, *a* represents an early stage of the change, and *b* part of a large space, as seen with No. 7, Hartnack.)

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[1] This paper was written before the publication of the *Journal of Anatomy and Physiology* for July 1881, and therefore contains no reference to an article by Dr Vincent Harris and Mr Alban Doran on the "Ovary in Incipient Cystic Disease. But I have added a note to explain the reasons why I differ from their conclusions in a part of their article.

Not unfrequently associated with this change in the ovary is another entirely distinct from it, which may be briefly alluded to here to prevent errors in observation. In some of the transparent spots mentioned at the beginning of this paper, there is no deposition of a new substance, but simply a destructive rarefaction of the stroma, together with the formation of branching cells with long processes; a fine web of delicate filaments is seen in these spaces; some of the filaments are apparently derived from the tissue of the stroma, others are prolonged from the branching cells; within the meshes we find altered blood and large granular bodies with distinct nuclei. The spaces seem to grow rapidly, they contain no vessels which can be recognised, and their centre always breaks down in a short time into a mass of *débris*. I may add that in two or three instances I have found these filamentous patches bordered by stroma, which showed an infiltration of the colloid material; but beyond this apparently accidental association, the two processes seem to be essentially distinct. Whatever the significance of these structures may be, they have no connection with the subject of this paper.

With regard to the conditions under which the colloid change occurs, I can only speak from my own observations, having been unable to discover in any author a minute description of the change in the non-cystic ovary. (1) It is most frequently met with in the atrophied ovaries of women after the menopause. (2) The degeneration is often associated with chronic ovaritis or peri-ovaritis with adhesions. (3) It is occasionally seen in ovaries which have been the subjects of repeated and intense congestions, as indicated by follicular hæmorrhages, &c. (4) Lastly, I have found an early stage of the change in ovaries which in all other respects seemed normal. I have not as yet seen it in any ovary before the age of twenty. The specimens exhibiting the most advanced stage have been from elderly women. The degeneration is also met with in ovaries beginning to be cystic, and in the walls of cystomata; but with these cases I am not at present concerned.

In investigating the origin of the colloid patches, the first thing requisite is to discover their earliest form. Of course, the comparative size of the spaces as seen in a section is of no value in determining this point, since (1) the apparently small spaces may be in reality only parts of larger ones, and (2) the small may be older than the large, derived from them by a process of contraction. Bearing in mind, however, these and other obvious sources of error, it is easy to satisfy oneself by a series of sections through an affected ovary, that the youngest patches are those described above as of microscopic size, and traversed in all directions by a fine network of delicate stromal trabeculæ. This point having once been settled, it seems evident that the change does not originate in Graafian follicles, or in the fœtal glandular tubes of Pflüger and Waldeyer; since in the earliest stage the spaces are minutely subdivided by processes of ovarian tissue, and never show a vestige of lining epithelium. It is equally clear that the change is not an inflammatory one, in the ordinary sense of the term. Everything tends to show that the youngest spaces are produced either by infiltration of a new material, or by localised softenings of the intercellular substance. The latter view is the more probable. That the intercellular substance is the part primarily at all events affected, appears to be shown by the fact that the cells of stroma immediately bordering the spaces exhibit no change. With regard to the precise nature of the degenerative softening, it is hard to offer any definite opinion, the analysis of the substance being attended by considerable difficulties: the term "colloid" is used throughout this paper simply to indicate the formation of a semi-fluid or gelatinous product of degeneration which does not exhibit the mucoid reaction with acetic acid.

The following are briefly my conclusions as to the history of this process in the non-cystic ovary. The microscopic patches (which by the way are usually found in the neighbourhood of Graafian follicles of some size; never, I think in the zone of minute ovisacs near the surface, and never in the tunica albuginea;) grow slowly by the extension of the softening into the surrounding stroma, and by the junction of neighbouring patches. The growth spreads irregularly, so that after a time the space contains not only the minute primary trabeculæ, but also large portions of the stroma which have escaped the change. The fine trabeculæ persist for a considerable time, but at last for the most part disappear, leaving traces in the shape of obscure lines in the colloid mass. The growth of the spaces does not proceed indefinitely, but after a certain period comes to a stand-still; when this occurs, the surrounding stroma appears, as it were, to accommodate itself to the shape of the mass, and the borders assume a smooth, scalloped appearance, resembling in some measure (as already mentioned) a cyst wall. At the same time, it is common to find granular degeneration in the centre of the mass, and some cirrhosis of the ovarian tissue generally. As a rule, no further change occurs, save consecutive atrophy of the organ. Thus, an ovary in the final stage of this metamorphosis is usually small, hard, corrugated on the surface, and consists of a shell or envelope of dense tissue, enclosing a coarse framework which contains the colloid substance, and in the centre a fibrous core supporting the blood-vessels.

Structures similar to, or identical with, those above described, have long been recognised in cystic ovarian tumours. Rindfleisch's description of the appearances found in the wall of a cystoma of his second variety is of course well known. Even such an early writer on ovarian pathology as Kiwisch has given a minute account of a form of alveolar degeneration, which consists in a breaking up of the stroma into closely aggregated alveoli, enclosing a homogeneous substance of varying degrees of consistency. Again, Dr. C. G. Ritchie (*Contributions to Ovarian Physiology and Pathology*, 1865), describes "the variety of tumour in which the substance known as colloid is most frequently found" as originating in "a hypersecretion into the meshes of stroma which enclose the first trace of the Graafian vesicle," which "stromal meshes may break into each other, and form larger or smaller cavities."

It is to be noted that these and other observers refer only to appearances found in cystic tumours of some size, and assign importance to the colloid change as representing an early stage in the growth of the tumour. None of them, so far as I am aware, give us any reason to believe that they had observed the same phenomenon in the non-cystic ovary, or were at all aware of the great frequency of its occurrence. There is an obvious difficulty in accepting any theory of a degenerative process, pure and simple, producing a cyst greatly exceeding the normal dimensions of the affected organ. It is, however, impossible to prove that the colloid spaces may not under certain conditions acquire a secreting epithelium, and thus in process of time become true retention-cysts. This is undoubtedly Rindfleisch's view of the destiny of the transparent spots which he figures in the wall of a cystoma; and he even seems to represent an epithelial lining in some of the spots still very minute, and still traversed by stromal trabeculæ. This, however, is certainly not what takes place in ovaries such as I have described. My observations lead me to think that colloid softening is one of the commonest accidents which happen to the ovary; that it has no necessary connection with cyst-formation; that it may be found under certain conditions wherever the stroma exists, whether in the organ otherwise healthy, or in the wall of a cystoma; and that, whatever may be its ultimate destiny in the latter case, in the former it simply replaces the normal stroma by a product of degeneration, which, together with the commonly associated cirrhosis, tends to cut short the functional activity of the ovary, and finally to bring about atrophy.

Allusion has been made to a remarkable change in the blood-vessels associated with colloid degeneration of the ovary. The altered vessels are usually in the immediate neighbourhood of colloid patches of some size, and sometimes penetrate into their interior. In the most advanced stage the artery is so changed as to present the appearance of a solid cylinder without any lumen, the transverse section showing as in the fig. at *c*. Three zones are to be observed in these transverse sections; externally a thin layer of unstriped muscle, next a broad band of homogeneous material occasionally containing a few isolated muscle-cells, and in the centre a mass of nuclei heaped up in confusion, which seem to be derived from the endothelial coat. In the less advanced stages a lumen may be detected in the centre of the vessel. The change seems in all cases to have its origin between the muscular coat and the endothelium: the resulting clear material stains very deeply with eosin, so that the diseased vessel presents an appearance which immediately attracts the eye in sections prepared with that agent. The affected vessels are always arteries, from a size just visible to the naked eye down to that of the smallest arterioles. I have seen nothing to show whether the change commences in the former or the latter class; it is found equally advanced in both in the same specimen. The larger vessels entering at the hilus are never affected. I can offer no suggestion to throw light on the nature of the degeneration; it is certainly not amyloid, and bears no resemblance to the change in chronic Bright's disease; beyond the fact of staining with eosin just mentioned, I have found no characteristic reaction in the altered coat.

This arterial disease is so commonly associated with colloid degeneration, that I cannot remember having met with the latter without some evidence of the former, and the more advanced the colloid change the more the vessels in the neighbourhood seem to be affected. There would seem, therefore, to be some connection between the two phenomena; perhaps the vascular metamorphosis is secondary to the degeneration in the ovarian tissue, perhaps (and this appears more probable) the latter is due to the alteration in blood supply caused by the arterial disease. The connection is, however, by no means a necessary one, since the altered vessels are certainly to be found in ovaries which seem healthy, and in ovarian tumours of different kinds.

DESCRIPTION OF PLATE VIII.

a, a. Represent early stages of the change in the stroma.

b. Is part of a large colloid mass. Stromal trabeculæ of various sizes are seen passing some way into the interior.

c, c. Show arteries in an advanced stage of disease.

d. A vessel with lumen still distinct.

e. Represents part of a follicle of moderate size, containing some coagulated liquor folliculi.

Note.—The authors of the article on the "Ovary in Incipient Cystic Disease" (*Journal of Anatomy and Physiology*, July 1881), put forward the view that one variety of cyst originates in a process of abnormal involution of Graafian follicles, in which there is an active ingrowth from the surrounding stroma, and a long persistence of certain remains of the membrana propria. The description and figures of the bodies resulting from this process, correspond very closely with the appearances which in the foregoing paper I have ascribed to a degeneration of the stroma. I should be more certain of the identity of the phenomena, were it not for the authors' allusions to "opaque *tube-like* masses" in the spaces, an appearance which, after careful re-examination of my own sections, I have been unable to detect. Assuming, however, that we have both been observing the same structures, it is clear that our conclusions differ widely. I am not sure that I have quite followed the reasons which have convinced Dr Harris and Mr Doran of the intra-follicular origin of the colloid masses, an origin which they believe to have been overlooked by other observers; nor have I found in their article any reference to, or explanation of, the very minute spaces described above. Again, it is by no means clear to me how a process of "active ingrowth" of stroma into pre-existing spaces can have anything to do with cyst-formation; nor why, if we accept that view, it should not be easy to trace the steps of the process from these cystic bodies up to unmistakeable cysts. Indeed, I have been unable to find in the article any reason for believing that the spaces described are to be regarded as the origin of cysts, further than the fact that the authors have detected them in ovaries which "afforded presumptive evidence that they were in a state of incipient cystic disease"—a fact which cannot be held to prove much if similar structures are often found in ovaries which afford no such evidence. But I shall here confine myself to a very brief statement of the reasons why I cannot believe that the change, as I have observed it, has an intra-follicular origin, or is connected with the development of cystic tumours.

1. If the degeneration took place in Graafian follicles, one would expect to find various stages of the change in the same specimen or in a series of observations on different ovaries, *i.e.*, some follicles retaining an unmistakeable membrana granulosa while exhibiting an early formation of stromal ingrowths, &c., others showing a more advanced stage in the morbid involution, and so on, up to the appearance of *b* in the figure. I have not observed anything of the kind; on the contrary, the smallest, youngest degenerate patches are far smaller than follicles normally possessing a true membrana granulosa; they are far more minutely subdivided by delicate stromal trabeculæ than the larger spaces; and they never show a trace of lining membrane or epithelium. That a colloid change does take place in Graafian follicles undergoing retrograde metamorphoses is undoubtedly true; but the resulting appearances do not resemble those above described.

2. The question of the origin of cysts is one of such consequence in ovarian pathology, that there is a natural tendency to assign to all morbid appearances an importance as being somehow connected with cyst development. When my attention was first directed to these colloid patches, I was misled by this tendency, and described them as a form of embryo-cysts.[1] I have since been convinced of my error, for the following reasons:—*first*, because when the change occurs in a cystic ovary, the truly cystic parts bear no resemblance to the parts affected by the colloid degeneration; and *secondly*, because I have found the change most frequently in ovaries which were certainly not cystic, which afforded no reason for believing that they would ever have become so, and which were not the fellows of cystic tumours on the other side.

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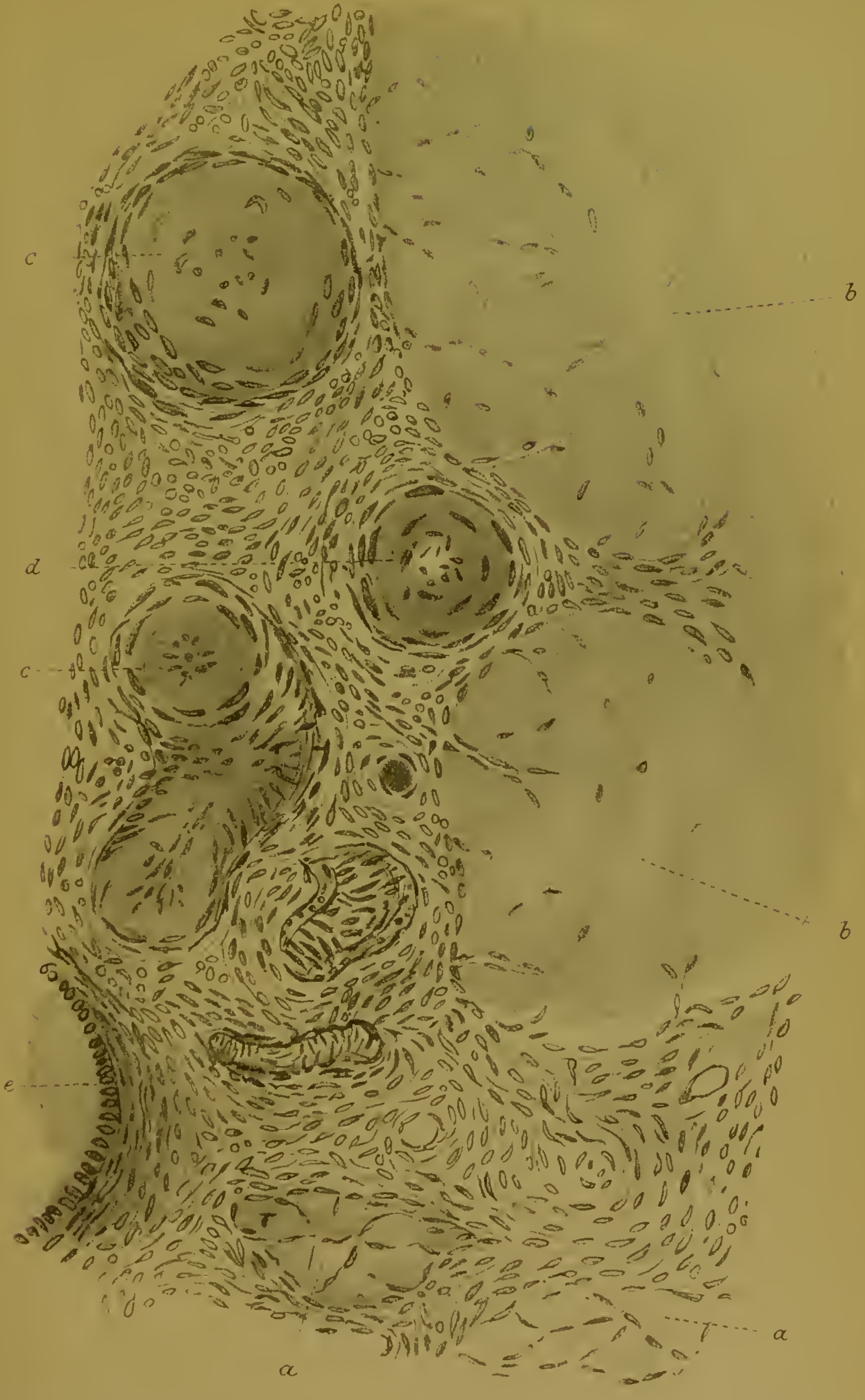
[1] In a description of the ovaries contributed to a report of a case of Oophorectomy, by Dr Heywood Smith, *British Medical Journal*, July 12, 1879.



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